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ARNE BRÄNDSTRÖM

On the anionoid and cationoid substitutions of metallic derivatives of β-ketoesters and related compounds

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On the Anionoid and Cationoid Substitutions of Metallic Derivatives of β-Ketoesters and Related Compounds

INAUGURAL DISSERTATION

BY

ARNE BRÄNDSTRÖM

FIL. LIC., NORRL.

BY DUE PERMISSION OF THE PHILOSOPHICAL FACULTY OF THE UNIVERSITY OF UPPSALA, TO BE PUBLICLY DISCUSSED IN THE LECTURE HALL OF THE INSTITUTE OF CHEMISTRY, MAY 8, 1954 AT 10 A.M., FOR THE DEGREE OF DOCTOR OF PHILOSOPHY. IN ADDITION TO THIS SURVEY THE PAPERS NUMBERED 1–14 IN THE LIST OF REFERENCES WILL BE PUBLICLY DISCUSSED.

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On the anionoid and cationoid substitutions of metallic derivatives of β-ketoesters and related compounds

By Arne Brändström

Introduction

The mechanisms for the Claisen condensation of ethyl acetate to give ethyl acetoacetate and the alkylation of this compound have been the subject of many investigations and of an even greater number of speculations for well-nigh a century. The mechanisms proposed are so many and the investigations published so numerous that the subject is too immense even for a person specialized in it. In this paper the mechanisms given by different authors will not be discussed, most of them having been collected by Henecka (15). Instead, the mechanisms for these two reactions will be considered in the light of some recent kinetic investigations by the present author and of the numerous experimental results of many other investigators, with Hauser *et al.* being the foremost among them.

Possible mechanism

In both the Claisen condensation and the alkylation reaction the structure of the metal (usually sodium) compound is of great interest. In the mechanisms given by most investigators the sodium compounds of β-ketoesters are a priori assumed to be of the ionic type. As pointed out by Brändström (1) this is far from correct, but although the chelate character of many sodium compounds has been clearly demonstrated by Sidgwick and Brewer (16) as early as 1925, very little has been done to use this to explain the Claisen condensation and the alkylation reaction.

Johnson (17) has assumed the existence of metal chelates in many reactions, but his theories have not been generally observed and accepted.

Hauser (18) mentioned a chelate mechanism as an alternative to the ionic mechanism proposed by him for the Claisen condensation, but preferred the latter as being the more simple in the absence of proofs for a chelate mechanism. In later papers (19, 20), however, Hauser prefers the chelate mechanism in the cases where magnesium and lithium compounds are used.

In the alkylation reaction, which is the more simple one to investigate, the reaction, in many cases, goes almost to completion with few side reactions. This and the possible formation of both O- and C-alkylation products makes it possible to choose between the ionic and the chelate mechanism from preparative results. This has been done by the present author (1) and the chelate mechanism so preferred for

the C-alkylation reaction has been proven to be correct by means of kinetic measurements (2).

In the Claisen condensation the yields are usually not very high and the side reactions numerous. The yields obtained by the condensation thus offer no evidence of mechanisms (21). Since the Claisen condensation is very hard to investigate by kinetic methods the question if the reaction mechanism is of the ionic or the chelate type must, up to the present time, be considered as unsettled. In some recent papers the present author has, however, made a kinetic investigation of the acidolysis of ethyl diacetoacetate and found that in all reactions studied the ester or its anion was coordinated to the metal ion (3–7). Since the reaction medium used was rather polar the same results must be applicable to the reaction of alcohol with metal derivatives of β-ketoesters and related compounds in the less polar media used in the Claisen condensation of which it is the retrograde reaction. The mechanism of the Claisen condensation can thus be predicted by means of the kinetic results obtained from the acidolysis of ethyl diacetoacetate and the principle of microscopic reversibility (22) which enables the mechanism of the forward reaction to be known with as much accuracy as the mechanism of the reverse reaction.

The ionic mechanism

A reaction of a pure ionic type is defined as one in which the reacting substances are not coordinated to the cation (2). From the kinetic results it can be concluded that an ionic mechanism exists in some alkylation reactions (1, 2) but not in anionoid reactions (7).

In the ionic alkylation reaction the alkyl group can enter at different points of the mesomeric ester anion with different products as a result. The proportion of the different products can be predicted from the property of the mesomeric anion and the halide used. As the principles for the reaction of mesomeric anions are extensively discussed in most textbooks of theoretical organic chemistry such a discussion is omitted here.

It must, however, be pointed out that the proportion of the different products found may sometimes not be the same as that initially formed because of subsequent reactions. Such an example is given by EISENHAUER and LINK (23) and their results have been discussed by BRÄNDSTRÖM (8).

The chelate alkylation mechanism

As found by the present author (1, 2) a chelate alkylation mechanism of tautomeric substances easily explains the C-alkylation of β-diketones and β-ketoesters. This type of reaction has been carefully treated by the present author (1, 2). It must, however, be pointed out that in a nonpolar solvent the 2-covalent alkali compounds which may be present represent such an unusual coordination structure that any comparison with the properties of alkali compounds in dilute aqueous solutions is unsound. This may explain the rather curious tendency of the alkali metals to form 2-covalent compounds in the order Li < Na < K (16).

In an alcoholic solution, on the other hand, the chelation tendency for the different alkali cations seems to follow the order expected Li > Na > K (2).

The unusual coordination tendency of the alkali ions in a nonpolar solvent may result in an unexpectedly high difference in the alkylation velocity of compounds containing different alkali cations. — An increasing ionic radius results both in a higher concentration of the chelate and an increase of its reactivity. — Such an effect has been observed by BRÄNDSTRÖM (9) and by CRONYN whose results have been discussed by MARTELL and CALVIN (24) and by BRÄNDSTRÖM (10).

In this connection it may be pointed out that the suggestion by MARTELL and CALVIN (24) that the formation of the enol often is the rate-determining step in the alkylation must be incorrect. If it was correct the alkylation velocity would be the same if different alkyl halides were used, which is not in agreement with the experimental results well known to most organic chemists.

The anionoid reactions

The acidolysis of ethyl diacetoacetate has been investigated using various metal compounds as catalysts. From the kinetic results it can be concluded that there are two possible mechanisms for the reaction:

1. The reaction takes place through a complex consisting of the metal chelate of ethyl diacetoacetate to which the acetic acid is coordinated.
2. The reaction takes place between the ester coordinated to the metal cation and a free acetate anion.

The first type of reaction was found for metal cations with a high chelation tendency, in which case the metal compound probably is present largely in the chelate form.

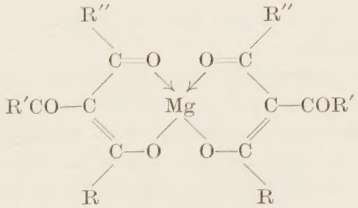
The second type, on the other hand, was found for the alkali compounds, which probably exist largely in an ionic form in the reaction mixture.

In no case studied was a pure ionic reaction found. This is of great interest since most anionoid reactions of preparative importance occur in solvents of a much lower polarity, with a corresponding higher tendency of the metal ion to form coordination compounds with the ketoester, than the acidolysis reaction. The mechanisms found for the acidolysis must hence be applicable to most anionoid attacks on the metal derivatives of tautomeric substances.

The acidolysis reaction

With magnesium oxide as a catalyst the acidolysis of ethyl diacetoacetate is of the first type and can be considered as an attack on the chelate by acetic acid coordinated to the cation (5, 7).

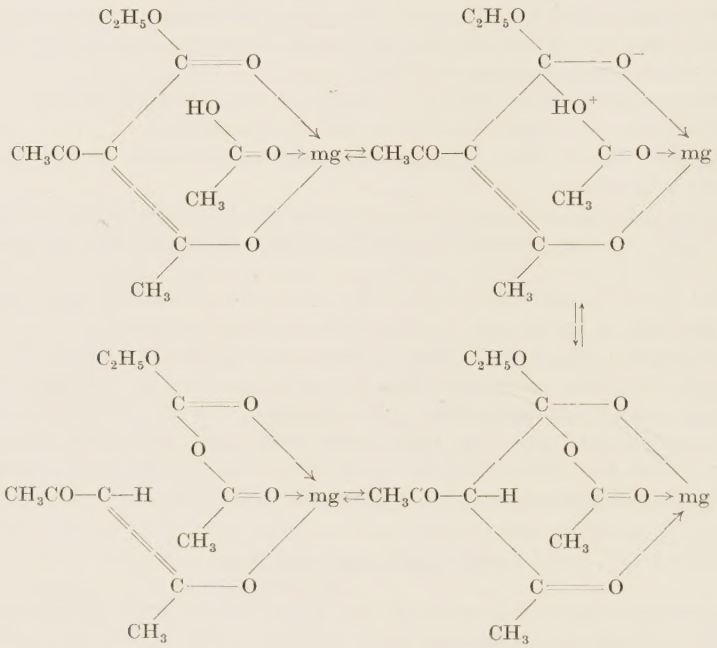
The chelate



has points of low electron density at the carbon atoms of the carbonyl groups. An anionoid attack of the chelate takes place at one of these points—which one depends

on the substituents on the carbonyl groups. As found by the present author (5) the velocity of the magnesium oxide catalysed acidolysis is affected by substituents in the same way as the acid catalysed hydrolysis of esters. We can thus expect that the bulk of the R groups is the main factor determining the point of attack. In the reaction of a diethyl acylmalonate $R' = R'' = OC_2H_5$ and R = alkyl an attack at one of the carboxyl groups leads to the formation of an acylacetate (11), whereas an attack at the carbonyl group may give rise to an acyl ecxhange (12). The acyl exchange can be expected to be most important if R is a small group such as methyl, and in fact a rapid acyl exchange was observed when diethyl acetylmalonate was heated with *n*-butyric or *iso*butyric acid (12). A similar acyl exchange was observed between ethyl diacetoacetate and *n*-butyric acid (3).

The magnesium oxide catalysed acidolysis of ethyl diacetoacetate has been formulated in the following way (mg represents one equivalent of magnesium):



In this mechanism the mixed anhydride of acetic acid and monoethyl carbonate is assumed to be the primary reaction product which is rapidly decomposed into carbon dioxide and ethyl acetate.

If the attack occurs at the carbonyl group the primary product is acetic anhydride, which if set free can function as a strong acetylation agent. In the reaction of a diethyl acylmalonate with the corresponding acid an attack at the carbonyl group results in an anhydride which may acylate the ketoester resulting from an attack at one of the carboxyl groups. The ethyl diacylacetate thus formed can then be acidolysed to give a diketone (13, 14). Since the relative extents of the carboxyl and carbonyl attacks of the diethyl acylmalonate determine the extent of the anhydride formed it can be concluded that a branching of the acyl group will result in a de-

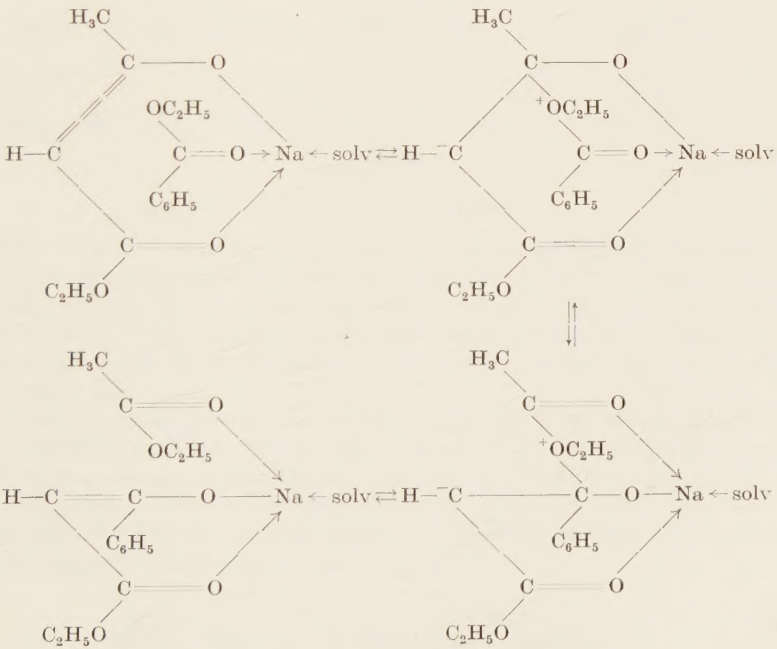
crease in the formation of the diketone. The present author (13) has very approximately determined the extent of this diketone formation for the reaction of different diethyl acylmalonates with the corresponding acid RCOOH and found the yields: R = CH_3CH_2, 12 %; R = $CH_3CH_2CH_2$, 11 %; R = $(CH_3)_2CH$, 1 %; and R = $(CH_3)_3C$, 0 %. These are in good agreement with the yields that can be expected from the relative velocities for the acid hydrolysis of the esters of the corresponding acids.

It is of interest to note that the formation of the ethyl diacylacetate can also result from a direct acylation of the ethyl acylacetate by means of the diethyl acylmalonate (13, 3). Which of these mechanisms is the correct one is hard to establish (8).

Another very interesting acyl group exchange has been observed by McElvain and Weber (25) in the reaction of the sodium compounds of some β-diketones and β-ketoesters with an ester. With ethyl acetoacetate and ethyl benzoate the net reaction is

$$[CH_3COCHCOOC_2H_5]Na + C_6H_5COOC_2H_5 \rightarrow [C_6H_5COCHCOOC_2H_5]Na + CH_3COOC_2H_5.$$

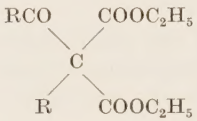
In this reaction we can expect that the sodium compound is present largely as the chelate which is soluble in the ester. From the fact that the reaction is much slower with diethyl malonate we can expect that the rate determining step of the reaction is an anionoid attack at the carbonyl group of the ketoester compound. The reaction can thus be formulated:

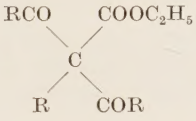


This mechanism explains why an attack preferentially takes place at the carbonyl group yielding a β-ketoester and not a β-diketone which would be the result of an attack at the carbethoxyl group.

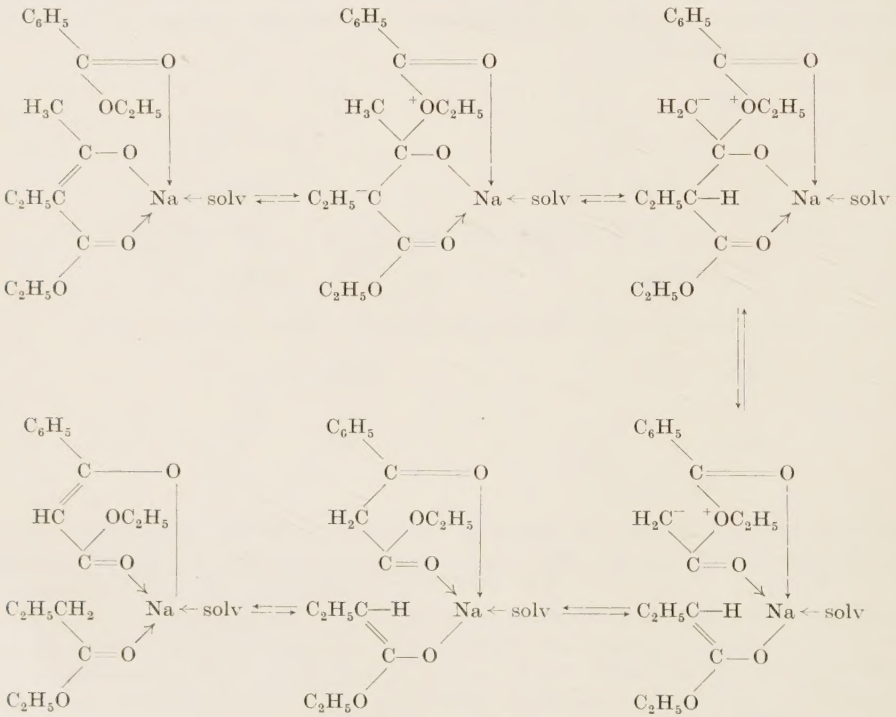
The mechanism proposed is very similar to the mechanism for the acyl exchange in the acidolysis of diethyl acetylmalonate.

As pointed out by the present author (3) the alkyl groups on the carbonyl carbon atoms of a chelate ring are points of high electron density. If the carbon atom between two carbonyl groups, which is usually the most important point of high electron density, is substituted by alkyl groups, the reactivity of this atom towards acylating agents is highly reduced. This can be seen from the fact that compounds of the types:





are cleaved by an alcoholic solution of sodium ethoxide even when cold (26). The anionoid reactivity of the methyl side-chain is, however, not hindered. The reaction of the sodium compound of ethyl ethylacetoacetate with ethyl benzoate may thus be formulated as:

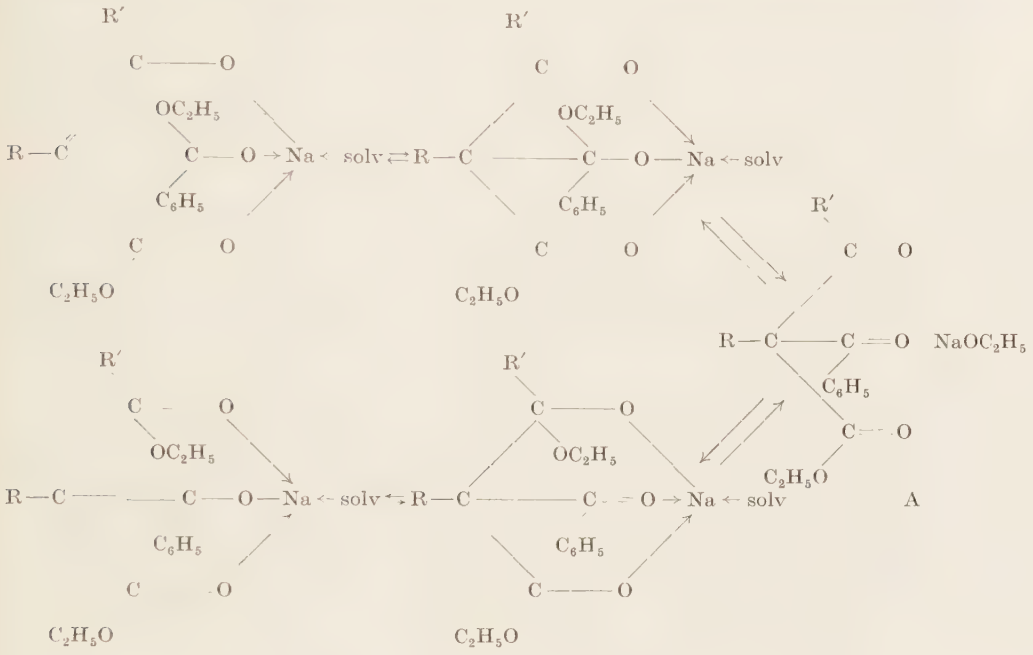


The products isolated in this reaction were ethyl benzoylacetate and ethyl *n*-butyrate in agreement with the mechanism suggested.

When the methyl side-chain also was substituted by alkyl groups as in ethyl

*iso*butyryl-*n*-butyrate the reaction products were ethyl ethylbenzoylacetate and ethyl *iso*butyrate. In this case the reaction obviously follows the same path as the reaction of ethyl acetoacetate and ethyl benzoate.

There are many arguments against the mechanism proposed by McElvain and Weber which was considered to involve at first a cationoid attack by the ester, thus:



The intermediate A is very improbable if R is an alkyl group because alkylated diacylacetates are very unstable towards sodium ethoxide. If it exists it must have a very short life and the first cationoid attack would be the rate determining step, but in this case diethyl malonate would react much more readily than ethyl acetoacetate in this reaction since the former is much more rapidly alkylated and acylated than the latter (1).

If the acylation is the first step it should be possible to isolate ethyl diacylacetates from the reaction mixture, but no such compounds were found although many attempts were made to isolate them. The alcohol formed in some reactions is by no means a proof for the mechanism given by McElvain and Weber since this may have been formed by some of the numerous side reactions which are possible, e.g. the formation of dehydracetic acid.

The mechanism for the Claisen condensation

The cleavage of β-ketoesters and related compounds with sodium ethoxide is of great interest as representing the reversal of the Claisen condensation. For the alcoholysis there are two mechanisms to be discussed. In one of them the ethoxide

ion attacks the ester and in the other the alcohol attacks the anion or chelate of the ester. As pointed out previously, no pure ionic mechanism has been found for the acidolysis of ethyl diacetoacetate. Since the reaction medium in a Claisen condensation usually has a low polarity it seems very plausible to postulate that the same is valid for the alcoholysis reaction too.

The similarity between the acidolysis and the alcoholysis reactions is easily seen from the following equations:

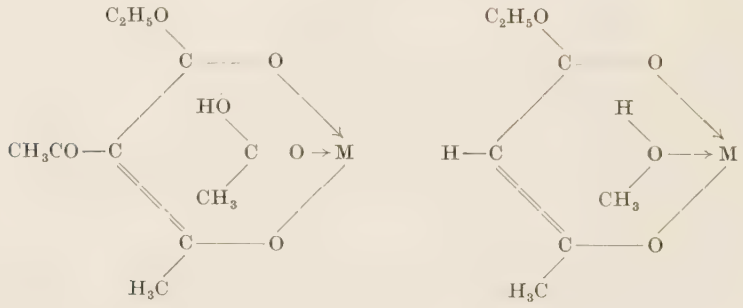
$$CH_3COCHCOOC_2H_5 + R'OH \xrightarrow{R'OM} CH_3COOR' + RCH_2COOC_2H_5$$

$$CH_3COCHCOOC_2H_5 + R'OH \xrightarrow{R'OM} CH_3COCH_2R + R'OCOOC_2H_5$$

With $R' = C_2H_5$ we have the two possible alcoholysis reactions and with $R' = CH_3CO$ we have the two acidolysis reactions, the acyl exchange and the decarbethoxylation reaction.

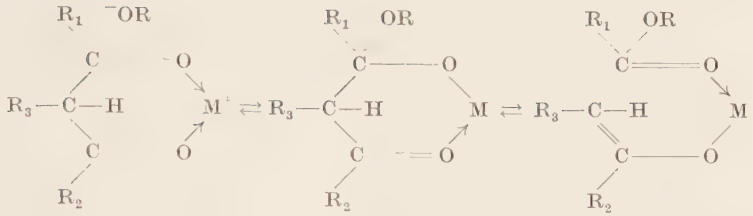
In applying the results obtained from the investigation of the acidolysis reaction to the alcoholysis reaction some interesting facts come to light.

An attack on the chelate of ethyl diacetoacetate by the acetic acid has been observed only when the acetic acid can be coordinated to the metal ion in the chelate. Such a coordination tends to place the acetic acid in a position suitable for the reaction with the carbonyl groups of the chelate. If alcohol on the other hand is coordinated to a chelate it is not in a position suitable for the reaction with the carbonyl groups. This difference can be seen from the following formulae:



By a comparison with the acidolysis reaction we can thus expect the ester chelate to react neither with the alcohol coordinated to the chelate nor with alcohol not coordinated to it. From this it can be concluded that there are no mechanisms by which the alcoholysis can take place as an attack on the chelate by the alcohol.

The alcoholysis reaction must then take place by an attack on the ester by an ethoxide ion. Since the corresponding mechanism for the acidolysis reaction has been observed and found to involve the ester coordinated to the cation, the mechanism for the alcoholysis reaction can be formulated as



A

By means of the principle of microscopic reversibility (22) it can be concluded that the intermediate A, "transition state" (27), is the same in the alcoholysis as in the reversed reaction which is the Claisen condensation.

The mechanism for the Claisen condensation so deduced from the kinetic results of the acidolysis of ethyl diacetoacetate is the same as the chelate mechanism given by HAUSER (18–20). Since this mechanism is carefully treated by HAUSER in his numerous papers on condensation it will not be discussed in any detail. It is, however, interesting to note that the kinetic results have given a somewhat deeper insight in the mechanism than a mechanism deduced from preparative results only.

The fact that the chelate (and the anion) of a ketoester is resistent to an attack of alcohol is the most important new fact which is available from kinetic measurements only. This gives an interesting aspect on some well-known experimental results. Since the chelate is resistent to an attack of alcohol, it can be concluded that the formation of the chelate decreases the concentration of the ketoester available for the alcoholysis reaction, with a corresponding decrease in the velocity of this reaction. There is no simple correlation between the ease of condensation of an ester and the chelation tendency for the resulting ketoester, with the consequence that a decrease in the velocity of the alcoholysis reaction due to the chelation does not necessarily give rise to a corresponding decrease in the velocity of the condensation. Due to the reversibility of the reaction, a decrease in the alcoholysis reaction without the corresponding decrease in the condensation reaction will give rise to a better yield of the condensation product.

The effect of different cations and the polarity of the solvent—two important factors for the chelation—on the yields in the Claisen condensation has been very little investigated (20).

The effect of different alkyl groups R in the condensation of esters of the type $RCH_2COOC_2H_5$ has been extensively investigated but no acceptable theory (18) has been advanced to explain why ethyl *iso*valerate ($R = (CH_3)_2CH$) is not self-condensed by means of sodium ethoxide even under forcing conditions (28). The result is, however, easily explainable from the fact that an *iso*propyl group decreases the chelation tendency of β-ketoesters and related compounds to a very high extent. It may be mentioned that acetylacetonates do not give the usual coloured chelates with cupric and ferric ions when the 3-position is substituted with an *iso*propyl group but give typical chelates when substituted with a straight chain alkyl group.

In the condensation of ethyl *iso*valerate by means of sodium ethoxide the ethyl *iso*-valeryl*iso*valerate that would result can accordingly not be transformed into the sodium chelate and is thus not withdrawn from the alcoholysis reaction. The yield of the condensation must then be very low, in good agreement with the experimental results.

The sodium (and potassium) compounds resulting from the self-condensation of esters are present in a chelate form, which can be seen from the fact that they are soluble in hydrocarbons such as benzene and toluene (29).

Summary

The mechanisms for the reaction of metallic derivatives of β-ketoesters and related compounds with cationoid and anionoid reagents have been discussed.

As an example of the attack by means of a cationoid reagent the alkylation has been mentioned. For this reaction both an ionic and a chelate mechanism has been observed.

The anionoid attacks by acids or their anions and by the ethoxide ion have been discussed.

The factors which make an attack by alcohol molecules improbable have been mentioned.

The mechanism for the Claisen condensation has been deduced and found in agreement with the chelate mechanism given by HAUSER.

An explanation for the fact that ethyl *iso*valerate is not self-condensed by means of sodium ethoxide has been given.

ACKNOWLEDGMENTS

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